Anemia, a common hematologic complication in human immunodeficiency virus (HIV)-infected patients, can be caused by mechanisms including infections, neoplasms, or drug treatment. Studies have consistently found anemia to be associated with reduced survival, even when potentially confounding factors were controlled for. Importantly, recovery from anemia has been shown to reduce this risk to approximately the same level as seen among patients never having had anemia. Although anemia traditionally has been treated with blood transfusions, recent studies have shown recombinant human erythropoietin (r-HuEPO) to be effective in elevating hematocrit values and reducing transfusion requirements in HIV-infected patients who have endogenous erythropoietin levels of ≤500 IU/L. Therapy with r-HuEPO has been shown to be safe and well tolerated. In a recent study, moreover, receipt of erythropoietin was associated with a decreased risk of death, whereas transfusion was associated with an increased risk. If these results are confirmed, the link between r-HuEPO and decreased risk of death in HIV-infected patients with anemia will be further strengthened.

Many of the factors that affect survival in HIV-infected persons are well known. Thus, plasma virus load, measured as concentration of HIV-1 RNA in plasma, and CD4\(^+\) cell count repeatedly have been shown to be strong, independent predictors of progression to AIDS and death [1–3]. Opportunistic infections have been a hallmark of AIDS; when CD4\(^+\) cell count was controlled for, several such infections, including Mycobacterium avium complex and cytomegalovirus infections, Pneumocystis carinii pneumonia, and toxoplasmosis, have been linked to an increased risk of death [4]. The age of the patient at onset of AIDS also affects time to death; when initial diagnosis, CD4\(^+\) cell count, and therapy were controlled for, patients ≥37 years of age at the onset of AIDS have been found to survive for significantly shorter time periods than do their younger counterparts [1].

The relationship between anemia and survival in HIV-infected patients has been the focus of recent investigation. Anemia may arise from any of several mechanisms in this patient population. For example, ineffective hematopoiesis or infectious and neoplastic diseases that often accompany HIV infection may result in anemia [5, 6]. In addition, drug therapy, particularly therapy with zidovudine, has been associated with an increased incidence of anemia [7–9]. Although anemia, except in severe cases, has frequently been viewed as affecting primarily the patient’s quality of life, several studies have found anemia to be associated with early death [1, 10–17]. Anemia may have a particularly widespread negative impact on survival because it is a common complication of AIDS [18].

Given the potential effect of anemia on survival among AIDS patients, this article reviews studies linking anemia and early death, evidence suggesting that recovery from anemia reduces this excess risk of death, and the use of recombinant erythropoietin as an alternative to transfusion for the treatment of anemia in HIV-infected persons.

**Anemia and Survival**

Several studies have demonstrated a negative relationship between anemia and survival, and recent research has estimated the relative risk of death associated with anemia (table 1) [1, 10, 11, 13, 14, 16, 17, 19].

In an open, multicenter study, Creagh-Kirk et al. [10] followed 4,805 AIDS patients treated with zidovudine (1,200 mg/day) for 44 weeks and evaluated associations between survival and several indicators of clinical status before treatment. Survival was positively associated with hemoglobin values stratified into four categories (<100 g/L, 100–109 g/L, 110–119 g/L, and ≥120 g/L). Overall, 83% of patients with baseline hemoglobin levels of ≥120 g/L survived to the end of the follow-up period, compared with just 56% of those with baseline hemoglobin levels of <100 g/L. The two groups having intermediate baseline hemoglobin levels also had intermediate survival rates. The authors concluded that the extent of anemia at initiation of zidovudine therapy is an important predictor of survival, a conclusion that would have been strengthened by the reporting of \( P \) values for differences in survival rates among groups.

A smaller (\( n = 58 \)) open, multicenter study of outcomes of AIDS patients receiving zidovudine (1,200 mg/day) followed...
patients for a mean of 26.5 weeks (range, 3–52 weeks) [14]. With baseline hemoglobin levels stratified into four categories (≤105 g/L, 106–114 g/L, 115–130 g/L, and >130 g/L), low hemoglobin levels were found to be associated with earlier progression to death (P < .001). This highly significant result in a relatively small sample that provided low power to detect differences suggests the existence of a very strong relationship between hemoglobin level and survival.

In an open study, Sathe et al. [13] evaluated the relationship between anemia and survival among 76 AIDS patients with (n = 54) or without (n = 22) disseminated Mycobacterium avium-intracellulare complex infection. Patients were followed for at least 1 year, during which each patient received zidovudine for no more than 6 weeks. Anemia was more profound in the group with M. avium-intracellulare complex infection than in the group without (mean hematocrit, 22.9% vs. 31.4%, respectively). The baseline hematocrit value was positively and significantly correlated with survival among patients with infection (P = .03) but not among those without infection. The authors postulated that severity of anemia probably reflects the disruption of the normal regulatory functions of T cells and macrophages.

Two multicenter, open studies evaluated factors affecting outcomes among homosexual or bisexual men with either AIDS (n = 308) [16] or AIDS-related complex (n = 235) [17] who received 1,200 mg/day of zidovudine. In the study of AIDS patients, follow-up continued for a median of 48 weeks, and hemoglobin levels at the beginning of the study were dichotomized as <11 g/dL vs. ≥11 g/dL; in the study of patients with AIDS-related complex, follow-up continued for a median of 102 weeks, with baseline hemoglobin levels dichotomized as <13 g/dL vs. ≥13 g/dL. Higher hemoglobin levels were associated with longer survival from study entry in the group with AIDS (P = .02); among patients with AIDS-related complex, higher hemoglobin levels were associated with both longer survival from study entry (P < .001) and somewhat longer survival from the development of AIDS (P = .08).

In a study of 421 Italian patients with AIDS who were followed for up to 30 months, a hemoglobin level of 8 to <11 g/dL was associated with a relative risk of dying of 1.9 (95% CI = 1.3–2.8) and a hemoglobin level of <8 g/dL was associated with a relative risk of dying of 2.9 (95% CI = 1.9–4.5) compared with patients having a hemoglobin level of ≥11 g/dL at the time of diagnosis of AIDS. This association was adjusted for CD4+ cell count and for a clinical severity measure, the Severity Index for Adults with AIDS [19].

Table 1. Studies of the relationship between anemia and survival in HIV-infected patients.

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Diagnosis</th>
<th>Definition of anemia</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creagh-Kirk et al. [10]</td>
<td>4,805</td>
<td>AIDS</td>
<td>Baseline Hgb level: &lt;100 g/L; 100–109 g/L; 110–119 g/L; &gt;120 g/L</td>
<td>Survival positively associated with Hgb level (P value not reported); 83% survival if Hgb level &gt;120 g/L vs. 56% if &lt;100 g/L</td>
</tr>
<tr>
<td>Steinberg et al. [14]</td>
<td>58</td>
<td>AIDS</td>
<td>Baseline Hgb level: ≤105 g/L; 106–114 g/L; 115–130 g/L; &gt;130 g/L</td>
<td>Low Hgb level associated with earlier death (P &lt; .001)</td>
</tr>
<tr>
<td>Sathe et al. [13]</td>
<td>76</td>
<td>AIDS and MAI (54); AIDS, no MAI (22)</td>
<td>Baseline HCT</td>
<td>MAI group: HCT positively correlated with survival (P = .03); no-MAI group: HCT not significantly correlated with survival</td>
</tr>
<tr>
<td>Swanson et al. [16]</td>
<td>308</td>
<td>AIDS</td>
<td>During study Hgb level: ≤11 g/dL; &gt;11 g/dL</td>
<td>Hgb level of ≤11 g/dL positively associated with survival (P = .02)</td>
</tr>
<tr>
<td>Swanson et al. [17]</td>
<td>235</td>
<td>ARC</td>
<td>Baseline Hgb level: ≤13 g/dL; &gt;13 g/dL</td>
<td>Higher Hgb level associated with longer survival from study entry (P &lt; .001) and longer survival from development of AIDS (P = .08)</td>
</tr>
<tr>
<td>Moore et al. [11]</td>
<td>863</td>
<td>AIDS (420); ARC (443)</td>
<td>Baseline HCT: ≤35%; &gt;35%</td>
<td>Higher Hgb level associated with increased risk of death (relative hazard = 1.56; P = .001)</td>
</tr>
<tr>
<td>Saah et al. [1]</td>
<td>886</td>
<td>AIDS</td>
<td>Hgb level within 6 mo before AIDS onset</td>
<td>Lower Hgb level associated with increased risk of death: death (relative hazard = 0.91 per 1 g/dL; P = .003)</td>
</tr>
<tr>
<td>Turner et al. [19]</td>
<td>421</td>
<td>AIDS</td>
<td>Baseline Hgb level: ≤11 g/dL; 8 to &lt;11 g/dL; ≤8 g/dL</td>
<td>Survival positively associated with survival (P = .03)</td>
</tr>
</tbody>
</table>

NOTE. ARC = AIDS-related complex; HCT = hematocrit; Hgb = hemoglobin; MAI = Mycobacterium avium-intracellulare complex infection.
before the onset of AIDS was associated with a decreased risk of death (relative hazard = 0.91 per 1 g/dL; \( P = .003 \)).

Despite variations in patient groups, anemia-defining criteria, potential causes of anemia (e.g., infection, drug-related), and follow-up periods, these studies consistently found anemia to be associated with reduced survival independent of other prognostic factors. The effect of recovery from anemia on survival, however, has only recently been examined.

**Recovery from Anemia and Reduced Risk of Death**

Results of an open, multicenter study that used data from the Adult and Adolescent Spectrum of HIV Disease Surveillance Project suggest that recovery from anemia substantially reduces this excess risk of death [15]. Medical records for 31,534 HIV-infected patients with at least one recorded hemoglobin concentration were reviewed; patients were followed for up to 6 years. Among the 13,315 patients with sufficient data for analysis, the 1-year incidence of anemia (hemoglobin level of <10 g/dL) was related to the clinical stage of the disease: 3.2% for those with HIV but not AIDS, 12.1% for patients with immunologic AIDS (CD4 cell count of <200/μL or CD4 cell percentage of <14%) but not clinical AIDS, and 36.9% for those with clinical AIDS. Overall, 2,222 patients (16.7%) had anemia at some time; 494 of these anemias (22.2%) were drug-related. Survival did not differ significantly between those who had drug-related anemia and those whose anemia was attributed to other causes.

Survival analyses were based on 19,213 patients [15]. Median survival from first CD4 cell count was longer among those without anemia at all levels of first CD4 cell count (risk ratio range, 1.4–2.5; \( P = .001 \) for all) [15]. This relationship between anemia and survival remained significant in multivariate analyses when factors including clinical AIDS, neutropenia, age, antiretroviral therapy, and thrombocytopenia were controlled for. Among the 3,203 patients for whom more than one hemoglobin measurement was available, 1,341 (41.8%) received either recombinant erythropoietin or blood transfusion, and 1,208 (37.7%) recovered from anemia. At all CD4 cell count categories, recovery from anemia was associated with an increased median length of survival and with a decreased risk of death (risk ratio range, 0.27–0.43; \( P = .001 \) for all) (figure 1). Importantly, in most CD4 cell count categories, mortality rates among those who recovered from anemia were similar to those among patients who never had developed anemia. The authors did not evaluate whether there were differences in outcomes between patients treated with transfusion and those treated with recombinant erythropoietin.

Although recovery from anemia traditionally has been accomplished primarily via transfusion, the effect of transfusions is at best a temporary correction and palliation. In addition, transfusions carry the risk of transfusion reaction and may transmit additional infections, such as cytomegalovirus infection or hepatitis [20]. Research also has suggested that transfusions may down-regulate immune function [21–23] and that the observed link between repeated blood transfusions and decreases in both ratios of helper to suppressor cells and natural killer cell activity may reflect a normal immune response to chronic alloantigenic stimulation [22]. If these results are confirmed, they would provide conclusive evidence that repeated transfusion, rather than improving the health of HIV-infected patients with anemia, inadvertently hastens the progress of their disease.

**Recombinant Human Erythropoietin as an Alternative to Transfusion**

Recombinant human erythropoietin (r-HuEPO) is now recognized as a valued treatment for anemia in HIV-infected patients [24–26]. Erythropoietin is a glycoprotein growth factor produced by the kidney in response to a feedback control system that monitors oxygen in renal blood flow. When a diminished amount of oxygen reaches the kidneys because of anemia, the normal result is a drive toward homeostasis in which synthesis of erythropoietin by the kidneys increases, often dramatically. Enhanced erythropoietin circulation to bone marrow stimulates stem cell activity, leading in turn to increased red blood cell production. In conditions in which the natural erythropoietin response is inadequate, supplementation with r-HuEPO has been shown to overcome anemias due to a variety of underlying diagnoses. These conditions include the most frequent form of anemia in HIV infection, anemia of chronic diseases, as well as drug- and neoplasm-induced anemias [25].

Studies that have demonstrated r-HuEPO to be an effective treatment for HIV-infected patients with anemia are summarized in table 2 [12, 20, 27–29].

An early randomized, double-blind, placebo-controlled trial by Fischl et al. [27] studied changes in hematocrit values and transfusion requirements and reports of adverse events among 63 AIDS patients with hematocrit values of ≤30% who were treated with r-HuEPO (\( n = 29 \)) or placebo (\( n = 34 \)) adminis-

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**Figure 1.** Effect of recovery from anemia on survival in HIV-infected patients stratified by CD4 cell counts. \( * P = .0001 \) for all CD4 cell categories (log rank); mos = months. From [15].
Baseline endogenous erythropoietin levels were ≤500 IU/L in 48 patients; all patients received zidovudine. After 12 weeks of therapy, patients with low baseline endogenous erythropoietin levels treated with r-HuEPO had greater increases in hematocrit (P = .0001) and required fewer units of blood transfused (P ≤ .05) than did those receiving placebo; there were no clinically significant differences in adverse events between groups. No benefits were seen among patients with baseline endogenous erythropoietin levels of >500 IU/L.

These data collected by Fischl et al. [27] were combined with those of three similar randomized, double-blind, placebo-controlled trials to yield a sample of 255 AIDS patients with hematocrit values of ≤30 who were receiving zidovudine [20]. Nearly 70% of patients (n = 177) had baseline endogenous erythropoietin levels of ≤500 IU/L. Therapy with r-HuEPO was administered either iv or sc three times per week for 12 weeks to 125 patients, while the remaining 130 patients received placebo. As in the study by Fischl et al. [27], patients with low endogenous erythropoietin levels at baseline who received r-HuEPO had a greater increase in hematocrit (P = .0002), and fewer required transfusions (P = .001), compared with those receiving placebo; quality of life improved somewhat as well among those receiving r-HuEPO (NS). No toxicity related to r-HuEPO therapy and no increase in the risk of opportunistic infection were observed. No significant improvements in efficacy measures were noted, however, among patients with baseline endogenous erythropoietin levels of >500 IU/L. The authors concluded that therapy with r-HuEPO is safe and can reduce transfusion requirements and increase hematocrit values in AIDS patients receiving zidovudine who develop anemia.

A large (n = 1,943), open, multicenter study of the efficacy of r-HuEPO included AIDS patients with hematocrit values of ≤30% and baseline endogenous erythropoietin levels of ≤500 IU/L [28]. r-HuEPO was administered subcutaneously six times per week at a mean starting dosage of 22,732 U/week and a mean dosage at 54 weeks of 32,574 U/week. Just over half of patients (57%) were receiving zidovudine therapy at baseline. The mean hematocrit value increased from 28.0% at baseline to 33.1% at 6–12 weeks, 33.8% at 18–24 weeks, and 34.8% at 48–54 weeks (P values were not reported). Although 39.6% of patients required transfusions during the baseline period, this percentage was reduced to 22.4%, 18.3%, and 13.4% in the 6-week periods ending at weeks 12, 24, and 48, respectively (P values were not reported). These reductions were paralleled by reductions in mean numbers of units of blood transfused per

### Table 2. Studies of the efficacy of recombinant human erythropoietin in HIV-infected and AIDS patients with anemia.

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Diagnosis</th>
<th>Baseline E-EPO level</th>
<th>Definition of anemia</th>
<th>r-HuEPO dosage</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fischl et al. [27]</td>
<td>63</td>
<td>AIDS</td>
<td>≤500 IU/L, n = 48;</td>
<td>HCT &lt; 30%</td>
<td>3/w for 12 w; 100 U/kg iv, n = 29; placebo, n = 34</td>
<td>Low baseline E-EPO: increases in HCT compared with placebo (P = .0001), fewer units transfused (P &lt; .05), no difference in adverse effects; high baseline E-EPO: no benefit</td>
</tr>
<tr>
<td>Henry et al. [20]</td>
<td>255</td>
<td>AIDS</td>
<td>≤500 IU/L, n = 177;</td>
<td>HCT &lt; 30%</td>
<td>3/w for 12 w; 100 U/kg iv or 100–200 U/kg sc, n = 125; placebo, n = 130</td>
<td>Low baseline E-EPO: increases in HCT compared with placebo (P = .0002), decreased need for transfusion (P = .001), quality of life improved slightly (NS), no difference in adverse effects; high baseline E-EPO: no benefit</td>
</tr>
<tr>
<td>Phair et al. [28]</td>
<td>1,943</td>
<td>AIDS</td>
<td>≤500 IU/L in all</td>
<td>HCT &lt; 30%</td>
<td>6/w; mean starting dosage = 22,732 U/w and at 54 w = 32,574 U/w</td>
<td>Increase in HCT in majority of patients at 6, 12, and 54 w; fewer patients required transfusions and fewer units transfused at 12, 24, and 48 w; treatment well tolerated</td>
</tr>
<tr>
<td>Revicki et al. [29]</td>
<td>251</td>
<td>AIDS</td>
<td>≤500 IU/L in all</td>
<td>HCT &lt; 30%</td>
<td>6/w; starting dosage = 24,000 U/w, could increase to 48,000 U/w after 18 w</td>
<td>Increase in HCT at 12 and 24 w (P &lt; .0001); activities of daily living improved in patients with corrected anemia compared with those having uncorrected anemia (P &lt; .05)</td>
</tr>
<tr>
<td>Moore et al. [12]</td>
<td>2,348</td>
<td>HIV-infected</td>
<td>Hgb level of &lt;9.5 g/dL, stratified into grades:</td>
<td>18% of patients with anemia received r-HuEPO and 79.1% received transfusions</td>
<td>Grade of anemia associated with survival (P = .001); receipt of r-HuEPO associated with decreased risk of death (P &lt; .045); receipt of transfusion associated with increased risk of death (P &lt; .005)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. E-EPO = endogenous erythropoietin; HCT = hematocrit; Hgb = hemoglobin; NA = not available; r-HuEPO = recombinant human erythropoietin.

* This combined analysis of four studies included the data from [27].
† This sample is a subset of that described in [28].
patient. The authors concluded that treatment with r-HuEPO was well-tolerated and that there was no evidence that such therapy adversely affected these AIDS patients.

Results of analyses of data for 251 (12.9%) of the 1,943 AIDS patients included in the above study strongly suggest that alleviating anemia improves quality of life. In this subgroup, hematocrit values increased after 12 and 24 weeks of r-HuEPO therapy \((P < .0001)\) [29]. Patients with corrected anemia (hematocrit of \(\geq 38\%) and no transfusion within the past month) showed improvement in energy, home management, role functioning, and health perceptions compared with patients whose anemia remained uncorrected \((P < .05)\).

Our recent study of 2,348 HIV-infected patients seen at the Johns Hopkins HIV Clinic between July 1989 and December 1996 confirmed the negative relationship between survival and anemia and examined the effect on survival of the method of treatment for anemia [12]. Anemia was defined as a hemoglobin level of \(< 9.5 \text{ g/dL} \) and was further stratified into four severity levels \((8.0 – 9.4 \text{ g/dL}, 7.0 – 7.9 \text{ g/dL}, 6.5 – 6.9 \text{ g/dL}, \text{and } < 6.5 \text{ g/dL})\). Overall, 498 patients \((21.3\%)\) developed anemia, and each successive grade of anemia increased the hazard of dying, with adjustment for covariates including CD4+ cell count, age \(< 40\) years, opportunistic infection, and antiretroviral use \((P < .001)\). Of patients with anemia, 18.2% \((91)\) received r-HuEPO administered sc and 79.1% received transfusions. The sc route of administration was used because it was more convenient and because injections of r-HuEPO result in more sustained plasma levels than do iv infusions [24]. Importantly, receipt of r-HuEPO was associated with a decreased risk of dying among patients with anemia when other variables were controlled for \((\text{relative hazard } = 0.68; 95\% \text{ CI } 0.46 – 0.98; P = .045)\), whereas transfusion was associated with an increased risk of dying \((\text{relative hazard } = 1.50; 95\% \text{ CI } 1.17 – 1.93; P = .003)\). Although we cannot rule out treatment selection bias in this nonrandomized study, these results suggest not only that r-HuEPO is effective in correcting anemia but also that it improves survival in HIV-infected patients.

Conclusions

Anemia is a common hematologic complication in HIV-infected patients. It may be caused by infections, neoplasms, or drug treatment—particularly by treatment with zidovudine. In addition to diminishing quality of life, anemia has been demonstrated to be associated with an increased risk of early death in these patients. Recovery from anemia, however, reduces this risk to approximately the same level as seen among patients never having had anemia.

Traditionally, anemia has been treated with blood transfusions. Recent studies have shown r-HuEPO to be effective in elevating hematocrit values and reducing transfusion requirements in AIDS patients with endogenous erythropoietin levels of \(\leq 500 \text{ IU/L} \). The therapy has not been found to be toxic, to increase the incidence of opportunistic infections, or to hasten the progress of AIDS. In fact, if the results of our recent research are confirmed, the link between r-HuEPO (but not transfusion) and reduction of death risk among HIV-infected patients with anemia will be strengthened. If that link is substantiated, pharmacoeconomic studies should be conducted of the relative cost-effectiveness of treating anemia in AIDS patients with r-HuEPO vs. transfusion.

Acknowledgment

The author wishes to thank Jane G. Murphy, Ph.D., for editorial assistance.

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